



#4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Platzek, et al.

Group Art Unit: TBA

Serial No.: 09/925,618

Examiner: TBA

Filed: August 10, 2001

For: USE OF PERFLUOROALKYL-CONTAINING METAL COMPLEXES AS
CONTRAST MEDIA IN MR-IMAGING FOR VISUALIZATION OF PLAQUE,
TUMORS AND NECROSES

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) Use according to claim 1, wherein the metal complexes are also used as MRI contrast media for visualization of infarcted and necrotic tissue.

4. (Amended) Use according to claim 1, wherein the metal complexes are also used as MRI contrast media for independent visualization of necroses and tumors.

8. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula I

R^F-L-K

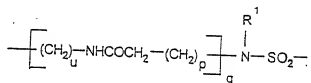
I

in which

R^F is a perfluorinated, straight-chain or branched carbon chain with formula $-C_nF_{2n}E_n$, in which

09925618-101801

- E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom and n stands for numbers 4-30,
- L means a direct bond, a methylene group, an -NHCO group, a group



whereby p means the numbers 0 to 10, and q and n, independently of one another, mean numbers 0 or 1, and

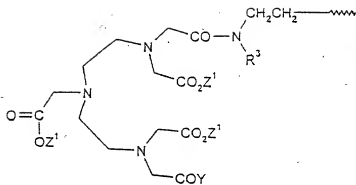
R³ is a hydrogen atom, a methyl group, a -CH₂-OH group, a -CH₂-CO₂H group or a C₂-C₁₅ chain, which optionally is interrupted by 1 to 3 oxygen atoms, 1 to 2 >CO groups or an optionally substituted aryl group and/or is substituted with 1 to 4 hydroxyl groups, 1 to 2 C₁-C₄ alkoxy groups, 1 to 2 carboxy groups, a group -SO₃H-,

or is a straight-chain, branched, saturated or unsaturated C₂-C₃₀ carbon chain, which optionally contains 1 to 10 oxygen atoms, 1 to 3 -NR^a groups, 1 to 2 sulfur atoms, a piperazine, a -CONR^a group, an -NR^aCO group, an -SO₂ group, an -NR^a-CO₂ group, 1 to 2 CO groups, a group -CO-N-T-N(R^a)-SO₂-R^F, or 1 to 2 optionally substituted aryls and/or is interrupted by these groups and/or is optionally substituted with 1 to 3 -OR^a groups, 1 to 2 oxo groups, 1 to 2 -NH-COR^a groups, 1 to 2 -CONHR^a groups, 1 to 2 -(CH₂)_p-CO₂H groups, 1 to 2 groups -(CH₂)_p-(O)_q-CH₂CH₂-R^F, whereby

R^a, R^F and p and q have the above-indicated meanings, and

T means a C₂-C₁₀ chain, which optionally is interrupted by 1 to 2 oxygen atoms or 1 to 2 -NHCO groups,

- K stands for a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides, specifically for a complexing agent or complex of general formula II

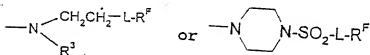


in which R^e , R^1 and B are independent of one another, and

R^e has the meaning of R^a or means $-(\text{CH}_2)_m\text{-L-R}^f$, whereby m is 0, 1 or 2, and L and R^f have the above-mentioned meaning,

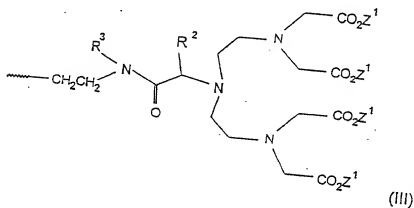
R^1 , independently of one another, mean a hydrogen atom or a metal ion equivalent of atomic numbers 22-29, 42-46 or 58-70,

B means $-\text{OR}^1$ or



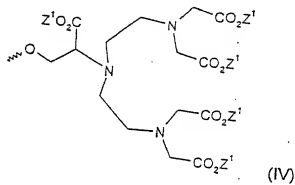
whereby R^1 , L, R^f and R^e have the above-mentioned meanings, or

K stands for a complexing agent or complex of general formula III



in which R^a and R^1 have the above-mentioned meanings and R^b has the meaning of R^a
or

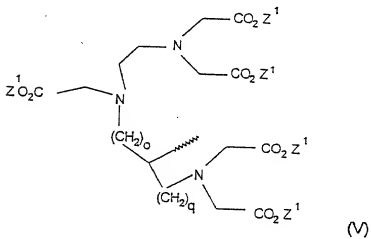
K stands for a complexing agent or complex of general formula IV



in which R^1 has the above-mentioned meaning

or

K stands for a complexing agent or complex of general formula V

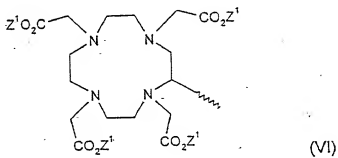


in which R^1 has the above-mentioned meaning, and o and q stand for numbers 0 or 1,

and yields the sum $o + q = 1$,

or

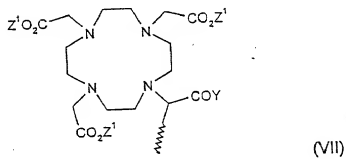
K stands for a complexing agent or complex of general formula VI



in which R^1 has the above-mentioned meaning

or

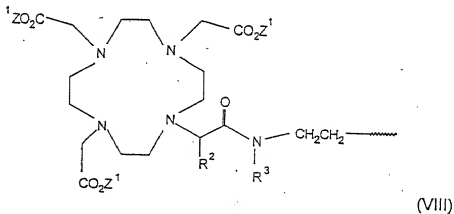
K stands for a complexing agent or complex of general formula VII



in which R^1 and B have the above-mentioned meanings

or

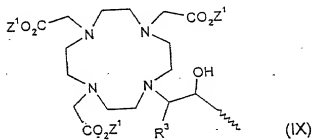
K stands for a complexing agent or complex of general formula VIII



in which R^c and R^1 have the above-mentioned meanings, and R^b has the above-mentioned meaning of R^a

or

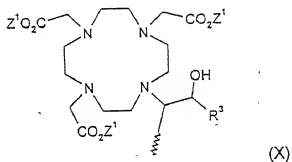
K stands for a complexing agent or complex of general formula IX



in which R^c and R^1 have the above-mentioned meanings,

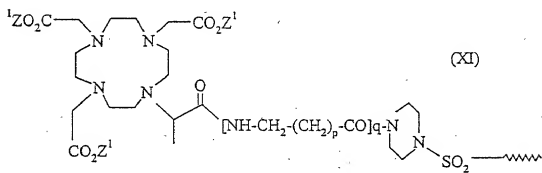
or

K stands for a complexing agent or complex of general formula X



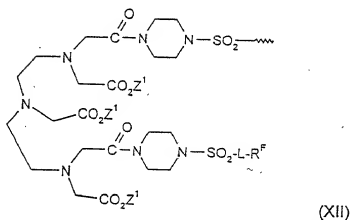
in which R^2 and R^1 have the above-mentioned meanings,
or

K stands for a complexing agent or complex of general formula XI



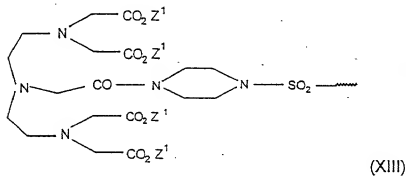
in which R^1 , p and q have the above-mentioned meanings, and R^b has the meaning of R^a ,
or

K stands for a complexing agent or complex of general formula XII



in which L, R^F and Z¹ have the above-mentioned meanings,
or

K stands for a complexing agent or complex of general formula XIII



in which R¹ has the above-mentioned meaning, are used.

10 (Amended) Use according to claim 8, wherein the compounds of formula I in which n in formula -C_nF_{2n}E stands for numbers 4-15 and/or E in this formula means a fluorine atom are used.

11. (Amended) Use according to claim 8, wherein the following compounds are used:

- Gadolinium complex of 10-[1-methyl-2-oxo-3-aza-5-oxo-{4-perfluorooctylsulfonyl-piperazin-1-yl}-pentyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17-heptaecafluoroheptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5,9-dioxo-9-{4-perfluorooctyl}-piperazin-1-yl]-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluorotetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,-16,16,17,17,18,18,19,19-henicosafuoro-nonadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-11-aza-11-(perfluorooctylsulfonyl)-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-8-phenyl-octyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraaza-cyclododecane.

12. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula Ia



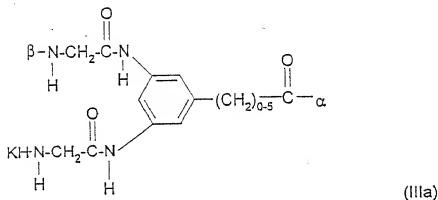
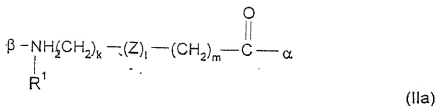
in which

- A is a molecule part that contains 2 to 6 metal complexes, which are bonded directly or via a linker to a nitrogen atom of an annular skeleton chain, and
- R^{F} is a perfluorinated, straight-chain or branched carbon chain with formula $\text{C}_n\text{F}_{2n}\text{E}$, in which

0925416-1

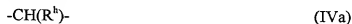
$$\begin{array}{c}
 \text{K} \\
 | \\
 \text{Y} \\
 | \\
 \text{N} \\
 | \\
 \text{K-Y-N} \quad \text{N-G-X-} \\
 | \\
 \text{N} \\
 | \\
 \text{Y} \\
 | \\
 \text{K}
 \end{array}$$

- q^1 is a number 0, 1, 2 or 3,
- K stands for a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides,
- X is a direct bond to the perfluoroalkyl group, a phenylene group or a C_1 - C_{10} alkylene chain, which optionally contains 1-15 oxygen atoms, 1-5 sulfur atoms, 1-10 carbonyl groups, 10-10 (NR^d) groups, 1-2 NR^dSO_2 groups, 1-10 $CONR^d$ groups, 1 piperidine group, 1-3 SO_2 groups and 1-2 phenylene groups or optionally is substituted by 1-3 radicals R^F , in which R^d stands for a hydrogen atom, a phenyl group, benzyl group or a C_1 - C_{15} alkyl group, which optionally contains 1-2 $NHCO$, 1-2 CO groups, 1-5 oxygen atoms and optionally is substituted by 1-5 Hydroxy, 1-5 methoxy, 1-3 carboxy, or 1-3 R^F radicals,
- V is a direct bond or a chain of general formula IIa or IIIa:



in which

- R^c is a hydrogen atom, a phenyl group, a benzyl group or a C_1 - C_7 alkyl group, which optionally is substituted with a carboxy group, a methoxy group or a hydroxy group,
- W is a direct bond, a polyglycol ether group with up to 5 glycol units, or a molecule part of general formula IVa



in which R^b is a C_1 - C_7 carboxylic acid, a phenyl group, a benzyl group or a $-(CH_2)_{1-5}$ -

NH-K group,

- α represents the binding to the nitrogen atom of the skeleton chain, β represents the binding to complexing agents or metal complex K,
- and in which variables k and m stand for natural numbers between 0 and 10, and l stands for 0 or 1

and whereby

- D is a CO or SO_2 group, are used.

20. (Amended) Use according to claim 12, wherein the compounds of general formula Ia in which the perfluoroalkyl chain is R^F - C_6F_{13} , - C_8F_{17} , - $C_{10}F_{21}$ or - $C_{12}F_{25}$ are used.

21. (Amended) Use according to claim 12, wherein the gadolinium complex of 1,4,7-

tris{1,4,7-tris(N-(carboxylatomethyl)-10-[N-1-methyl-3,6-diaza-2,5,8-trioxooctane-1,8-diyl])-1,4,7,10-tetraazacyclododecane, Gd complex}-10-[N-2H,2H,4H,4H,5H,5H-3-oxa-perfluorotridecanoyl]-1,4,7,10-tetraazacyclododecane is used.

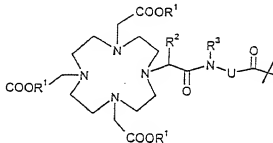
22. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula Ib



(Ib)

in which

K means a complexing agent or a metal complex of general formula IIb



(IIb)

whereby

R^1 stands for a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70,

R^2 and R^3 stand for a hydrogen atom, a C_1 - C_7 alkyl group, a benzyl group, a phenyl group, $-\text{CH}_2\text{OH}$ or $-\text{CH}_2-\text{OCH}_3$,

U² stands for radical L¹, whereby L¹ and U², independently of one another, can be the same or different,

A¹ means a hydrogen atom, a straight-chain or branched C₁-C₃₀ alkyl group, which optionally is interrupted by 1-15 oxygen atoms, and/or optionally is substituted with 1-10 hydroxy groups, 1-2 COOH groups, a phenyl group, a benzyl group and/or 1-5 -OR⁹ groups, with R⁹ in the meaning of a hydrogen atom or a C₁-C₇ alkyl radical, or -L¹-R^F,

L¹ means a straight-chain or branched C₁-C₃₀ alkylene group, which optionally is interrupted by 1-10 oxygen atoms, 1-5 -NH-CO groups, 1-5 -CO-NH groups, by a phenylene group optionally substituted by a COOH- group, 1-3 sulfur atoms, 1-2 -N(B¹)-SO₂ groups and/or 1-2 -SO₂-N(B¹)-groups with B¹ in the meaning of A¹, an NHCO group, a CONH group, an N(B¹)-SO₂ group or an -SO₂-N(B¹) group and/or optionally is substituted with radical R^F, and

R^F means a straight-chain or branched perfluorinated alkyl radical of formula C_nF_{2n}E, whereby n stands for number 4-30, and

E stands for a terminal fluorine atom, chlorine atom, bromine atom, iodine atom or a hydrogen atom,

and optionally present acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides, are used.

29. (Amended) Use according to claim 22, wherein the following compounds are used:

- 1,4,7-Tris(carboxylatomethyl)-10-(3-aza-4-oxo-hexan-5-yl)-acid-(2,3-dihydroxypropyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide]-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)acid-N-(3,6,9,12,15-pentaoxa)-hexadecyl)-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide]-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)-acid-N-5-hydroxy-3-oxa-pentyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide]-

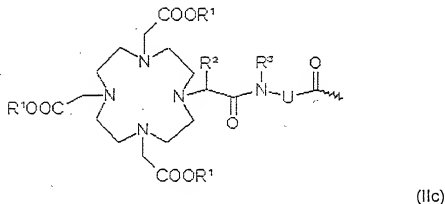
- 1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-{(3-aza-4-oxo-hexan-5-yl)-acid-[N-3,6,9,15-tetraoxa-12-aza-15-oxo-C₁₇-C₂₆-hepta-decafluor)hexacosyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-{(3-aza-4-oxo-hexan-5-yl)-acid-N-(2-methoxyethyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex.

30. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, the compounds with sugar radicals of general formula Ic



in which

- R represents a mono-or oligosaccharide radical bonded by the 1-OH- or 1-SH-position,
- R^F is a perfluorinated, straight-chain or branched carbon chain with the formula -C_nF_{2n}E, in which E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom, and n stands for numbers 4-30,
- K stands for a metal complex of general formula IIc,



in which

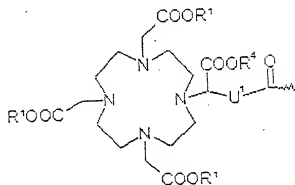
R^1 means a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70, provided that at least two R^1 stand for metal ion equivalents,

R^2 and R^3 , independently of one another, represent hydrogen, C_1 - C_7 alkyl, benzyl, phenyl, $-CH_2OH$ or $-CH_2OCH_3$, and

U represents $-C_6H_4-O-CH_2-\omega$, $-(CH_2)_{1.5}-\omega$, a phenylene group, $-CH_2-NHCO-CH_2-CH(CH_2COOH)-C_6H_4-\omega$, $-C_6H_4-(OCH_2CH_2)_{0.1}-N(CH_2COOH)-CH_2-\omega$, or a C_1 - C_{12} alkylene group or C_7 - C_{12} - C_6H_4-O group optionally interrupted by one or more oxygen atoms, 1 to 3 $-NHCO$ groups or 1 to 3 $-CONH$ groups and/or substituted with 1 to 3 $(CH_2)_{0.5}$ COOH groups, whereby ω stands for the binding site to $-CO-$,

or

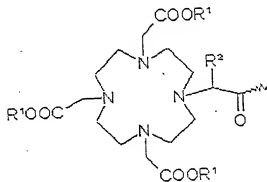
of general formula IIIc



(IIIc)

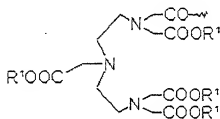
in which R^1 has the above-mentioned meaning, R^4 represents hydrogen or a metal ion equivalent mentioned under R^1 , and U^1 represents $-C_6H_4-O-CH_2-\omega$, whereby ω means the binding site to $-CO-$,

or of general formula IVc

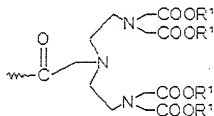


(IVc)

in which R^1 and R^2 have the above-mentioned meaning or of general formula VcA or VcB

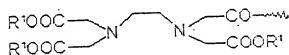


(VcA)



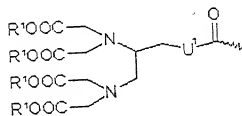
(VcB)

in which R^1 has the above-mentioned meaning, or of general formula VIc



(VIc)

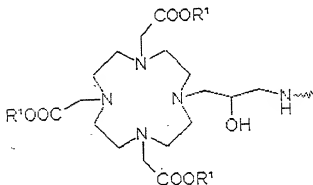
in which R^1 has the above-mentioned meaning, or of general formula VIIc



(VIIc)

in which R^1 has the above-mentioned meaning, and

U^1 represents $-C_6H_4-O-CH_2-\omega$, whereby ω means the binding site to $-CO-$ or of general formula VIIIc



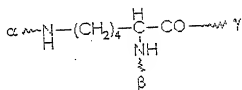
(VIIIc)

in which R^1 has the above-mentioned meaning,

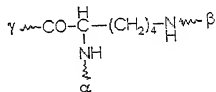
and in radical K, optionally present free acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides,

G for the case that K means metal complexes IIc to VIc represents a radical that is functionalized in at least three places and is selected from the following radicals a) to j)

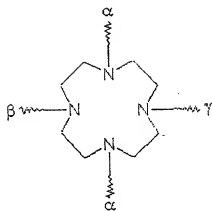
(a)



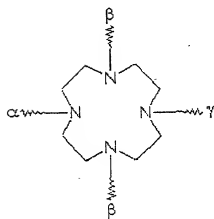
(b)



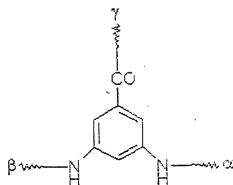
(c)



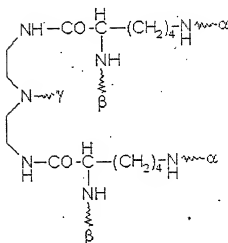
(d)



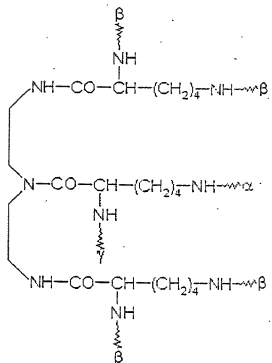
(e)



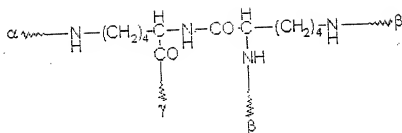
(f)



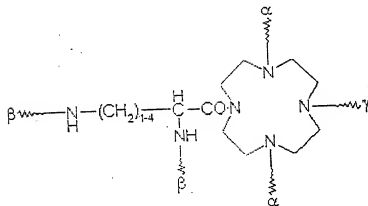
(g)



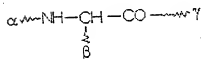
(h)



(i)



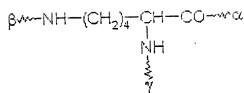
(j)



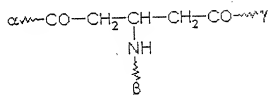
and

G for the case that K means metal complex VIIIc represents a radical that is functionalized in at least three places and is selected from k) or l),

(k)



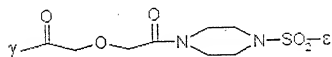
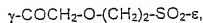
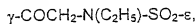
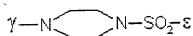
(l)



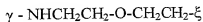
whereby α means the binding site of G to complex K, β is the binding site of G to radical Y, and γ represents the binding site of G to radical Z,

Y means $-\text{CH}_2$, $\delta - (\text{CH}_2)_{(1-5)}\text{CO}-\beta$, $\delta - \text{CH}_2 - \text{CHOH} - \text{CO}-\beta$ or $\delta - \text{CH}(\text{CHOH} - \text{CH}_2\text{OH}) - \text{CHOH} - \text{CHOH} - \text{CO}-\beta$, whereby δ represents the binding site to sugar radical R and β is the binding site to radical G,

Z stands for



or



whereby γ represents the binding site of Z to radical G, and ξ means the binding site of Z to perfluorinated radical R^{F}

and

l^1 , m^1 , independently of one another, mean integers 1 or 2, and

p^1 means integers 1 to 4, are used.

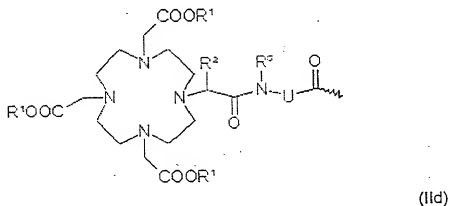
37. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, the compounds with polar radicals of general formula Id



in which

R^{F} is a perfluorinated, straight-chain or branched carbon chain with formula $-\text{C}_n\text{F}_{2n}\text{E}$, in which E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom, and n stands for numbers 4-30,

K stands for a metal complex of general formula IId,



in which

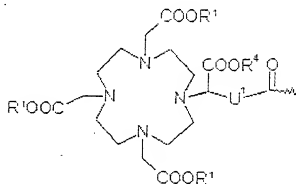
R^1 means a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70, provided that at least two R^1 stand for metal ion equivalents,

R^2 and R^3 , independently of one another, represent hydrogen, C_1 - C_7 alkyl, benzyl, phenyl, $-CH_2OH$ or $-CH_2OCH_3$, and

U represents $-C_6H_4-O-CH_2-\omega$ -, $-(CH_2)_{1.5}-\omega$ -, a phenylene group, $-CH_2-NHCO-CH_2-CH(CH_2COOH)-C_6H_4-\omega$ -, $-C_6H_4-(OCH_2CH_2)_{0-1}-N(CH_2COOH)-CH_2-\omega$ -, or a C_1 - C_{12} alkylene group or C_7 - C_{12} - C_6H_4-O group optionally interrupted by one or more oxygen atoms, 1 to 3 $-NHCO$ groups, 1 to 3 $-CONH$ groups and/or substituted with 1 to 3 $-(CH_2)_{0.5}COOH$ groups, whereby ω stands for the binding site to $-CO-$,

or

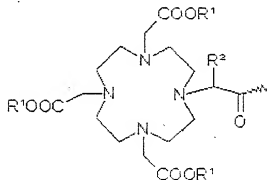
of general formula III d



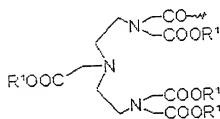
(III d)

in which R^1 has the above-mentioned meaning, R^4 represents hydrogen or a metal ion equivalent mentioned under R^1 , and U^1 represents $-C_6H_4-O-CH_2-\omega$ -, whereby ω means the binding site to $-CO-$, or

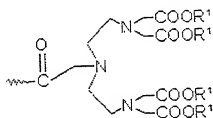
of general formula IV d



in which R^1 and R^2 have the above-mentioned meaning, or of general formula VdA or VdB

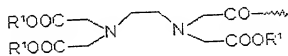


(VdA)



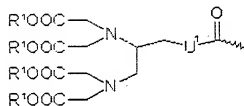
(VdB)

in which R^1 has the above-mentioned meaning, or of general formula VIId



(VIId)

in which R^1 has the above-mentioned meaning, or of general formula VIId



(VIId)

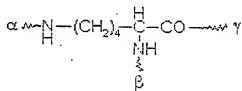
in which R¹ has the above-mentioned meaning, and

U¹ represents -C₆H₄-O-CH₂-ω-, whereby ω means the binding site to -CO-,

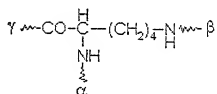
and in radical K, optionally present free acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides,

G represents a radical that is functionalized in at least three places and is selected from the following radicals a) to g)

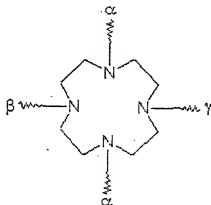
(a)



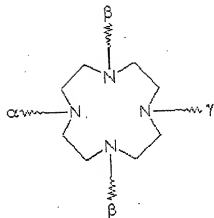
(b)



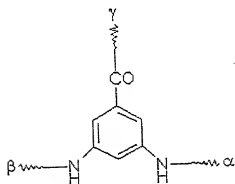
(c)



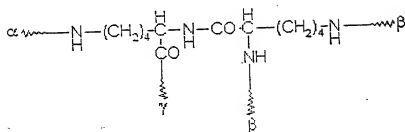
(d)



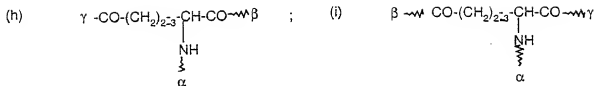
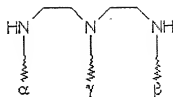
(e)



(f)

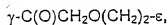


(g)



whereby α means the binding site of G to complex K, β is the binding site of G to radical R, and γ represents the binding site of G to radical Z

Z stands for



whereby γ represents the binding site of Z to radical G and ξ means the binding site of Z to perfluorinated radical R_f ,

R represents a polar radical that is selected from complexes K of general formulas IIId to VIId, whereby R^1 here means a hydrogen atom or a metal ion equivalent of atomic numbers 20, 23-29, 42-46 or 58-70, and radicals R^2 , R^3 , R^4 , U and U^1 have the above-indicated meaning,

or

means the folic acid radical

or

means a carbon chain with 2-30 C atoms that is bonded to radical G via -CO-, or SO₂- or a direct bond and is straight or branched, saturated or unsaturated, optionally interrupted by 1-10 oxygen atoms, 1-5 -NHCO groups, 1-5 -CONH groups, 1-2 sulfur atoms, 1-5 -NH groups or 1-2 phenylene groups, which optionally can be substituted with 1-2 OH groups, 1-2 NH₂ groups, 1-2 -COOH groups, or 1-2 -SO₃H groups, or

optionally substituted with 1-8 OH groups, 1-5 -COOH groups, 1-2 SO₃H groups, 1-5 NH₂ groups, 1-5 C₁-C₄ alkoxy groups, and

l¹, m¹, p², independently of one another, mean integers 1 or 2 are used.

44. (Amended) Use according to claim 37, wherein the gadolinium complex of 2,6-N,N'-bis[1,4,7-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecane-10-(pentanoyl-3-aza-4-oxo-5-methyl-5-yl)]-lysine-[1-(4-perfluorooctylsulfonyl)-piperazine]-amide is used.


45. (Amended) Use according to claim 1, wherein as perfluoroalkyl-containing metal complexes, galenical formulations that contain paramagnetic, perfluoroalkyl-containing metal complexes of general formulas I, Ia, Ib, Ic and/or Id and diamagnetic perfluoroalkyl-containing substances, preferably dissolved in an aqueous solvent, are used.

REMARKS

The amendments to the application are made to remove the multiple dependency of the claims and to make minor typographical errors. It is respectfully submitted that no new matter has been added and the amendment should be allowed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

 (Reg. No. 32542)
~~Dr~~ Anthony J. Zelano 27,869
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: SCH-1774

Date: December 18, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) Use according to claim 1 [or 2], wherein the metal complexes are also used as MRI contrast media for visualization of infarcted and necrotic tissue.

4. (Amended) Use according to claim [one of claims] 1 [to 3], wherein the metal complexes are also used as MRI contrast media for independent visualization of necroses and tumors.

8. (Amended) Use according to claim [one of claims] 1 [to 7], wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula I



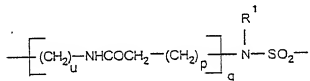
I

in which

R^F is a perfluorinated, straight-chain or branched carbon chain with formula $-C_nF_{2n}E$, in which

E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom and n stands for numbers 4-30,

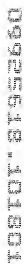
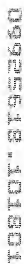
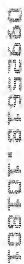
L means a direct bond, a methylene group, an $-NHCO$ group, a group



[(Please change R^1 to R^a in the formula!)]

whereby p means the numbers 0 to 10, and q and n, independently of one another, mean numbers 0 or 1, and

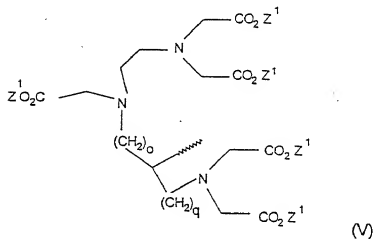




in which R^1 has the above-mentioned meaning

or

K stands for a complexing agent or complex of general formula V

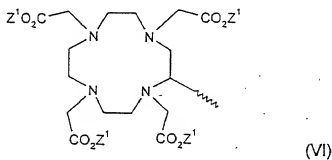


in which R^1 has the above-mentioned meaning, and o and q stand for numbers 0 or 1,

and yields the sum $o + q = 1$,

or

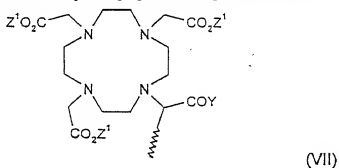
K stands for a complexing agent or complex of general formula VI



in which R^1 has the above-mentioned meaning

or

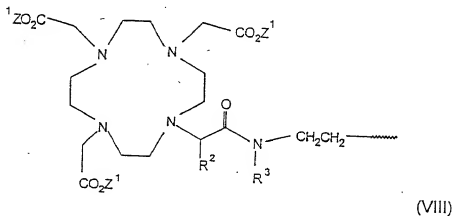
K stands for a complexing agent or complex of general formula VII



in which R¹ and B have the above-mentioned meanings

or

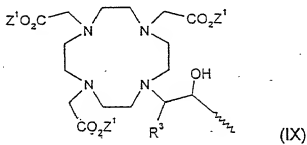
K stands for a complexing agent or complex of general formula VIII



in which R^e and R¹ have the above-mentioned meanings, and R^b has the above-mentioned meaning of R^a

or

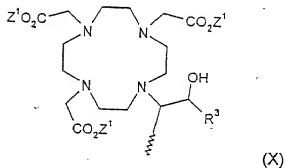
K stands for a complexing agent or complex of general formula IX



in which R^c and R^1 have the above-mentioned meanings,

or

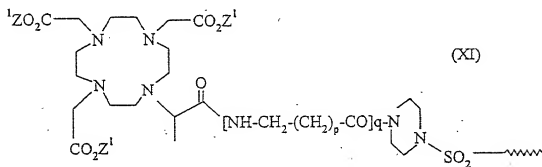
K stands for a complexing agent or complex of general formula X



in which R^c and R^1 have the above-mentioned meanings,

or

K stands for a complexing agent or complex of general formula XI

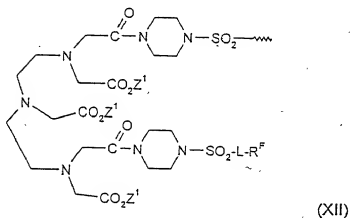


in which R^1 , p and q have the above-mentioned meanings, and R^b has the meaning of

R^a ,

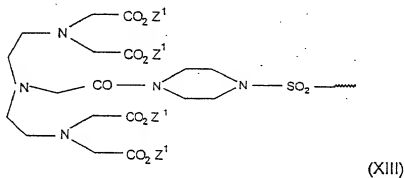
or

K stands for a complexing agent or complex of general formula XII



in which L, R^F and Z¹ have the above-mentioned meanings,
or

K stands for a complexing agent or complex of general formula XIII



in which R¹ has the above-mentioned meaning, are used.

10 (Amended) Use according to claim 8 [or 9], wherein the compounds of formula I in which n in formula -C_nF_{2n}E stands for numbers 4-15 and/or E in this formula means a fluorine atom are used.

11. (Amended) Use according to claim [one of claims] 8 [to 10], wherein the following compounds are used:

- Gadolinium complex of 10-[1-methyl-2-oxo-3-aza-5-oxo-{4-perfluorooctylsulfonyl-piperazin-1-yl}-pentyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17-heptadecafluoroheptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5,9-dioxo-9-{4-perfluorooctyl}-piperazin-1-yl]-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluorotetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,-16,16,17,17,18,18,19,19-henicosafuoro-nonadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-11-aza-11-(perfluorooctylsulfonyl)-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
- Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluorooctylsulfonyl)-8-phenyl-octyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

12. (Amended) Use according to claim [one of claims] 1[-7], wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula Ia

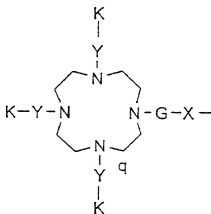


in which

- A is a molecule part that contains 2 to 6 metal complexes, which are bonded directly or via a linker to a nitrogen atom of an annular skeleton chain, and
- R^F is a perfluorinated, straight-chain or branched carbon chain with formula $C_nF_{2n}E$, in which

E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom, and n stands for numbers 4-30,

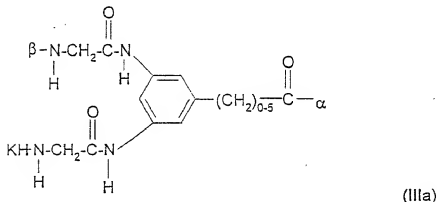
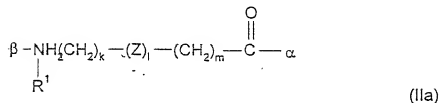
whereby molecule part A has the following structure:



whereby

- q^1 is a number 0, 1, 2 or 3,
- K stands for a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides,
- X is a direct bond to the perfluoroalkyl group, a phenylene group or a C_1-C_{10} alkylene chain, which optionally contains 1-15 oxygen atoms, 1-5 sulfur atoms, 1-10 carbonyl groups, 10-10 (NR^d) groups, 1-2 NR^dSO_2 groups, 1-10 $CONR^d$ groups, 1 piperidine group, 1-3 SO_2 groups and 1-2 phenylene groups or optionally is substituted by 1-3 radicals R^F , in which R^d stands for a hydrogen atom, a phenyl group, benzyl group or a C_1-C_{15} alkyl group, which optionally contains 1-2 NHCO, 1-2 CO groups, 1-5 oxygen atoms and optionally is substituted by 1-5 Hydroxy, 1-5 methoxy, 1-3 carboxy, or 1-3 R^F radicals,

- V is a direct bond or a chain of general formula IIa or IIIa:



in which

- R^a is a hydrogen atom, a phenyl group, a benzyl group or a $\text{C}_1\text{-C}_7$ alkyl group, which optionally is substituted with a carboxy group, a methoxy group or a hydroxy group,
- W is a direct bond, a polyglycol ether group with up to 5 glycol units, or a molecule part of general formula IVa



in which R^b is a $\text{C}_1\text{-C}_7$ carboxylic acid, a phenyl group, a benzyl group or a $-(\text{CH}_2)_{1-5}$ -

NH-K group,

- α represents the binding to the nitrogen atom of the skeleton chain, β represents the binding to complexing agents or metal complex K,
- and in which variables k and m stand for natural numbers between 0 and 10, and l stands for 0 or 1

and whereby

- D is a CO or SO_2 group, are used.

20. (Amended) Use according to claim [one of claims] 12 [to 19], wherein the compounds of general formula Ia in which the perfluoroalkyl chain is R^F -C₆F₁₃, -C₈F₁₇, -C₁₀F₂₁ or -C₁₂F₂₅ are used.

21. (Amended) Use according to claim [one of claims] 12 [to 20], wherein the gadolinium complex of 1,4,7-tris{1,4,7-tris[N-(carboxylatomethyl)-10-[N-1-methyl-3,6-diaza-2,5,8-trioxooctane-1,8-diyl)]-1,4,7,10-tetraazacyclododecane, Gd complex}-10-[N-2H,2H,4H,4H,5H,5H-3-oxa-perfluorotridecanoyl]-1,4,7,10-tetraazacyclododecane is used.

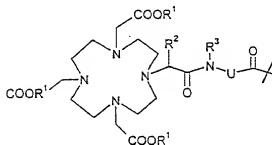
22. (Amended) Use according to claim [one of claims] 1 [to 7], wherein as perfluoroalkyl-containing metal complexes, the compounds of general formula Ib



(Ib)

in which

K means a complexing agent or a metal complex of general formula IIb



(IIb)

whereby

R¹ stands for a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70,

R² and R³ stand for a hydrogen atom, a C₁-C₇ alkyl group, a benzyl group, a phenyl group, -CH₂OH or -CH₂-OCH₃,

U² stands for radical L¹, whereby L¹ and U², independently of one another, can be the same or different,

A¹ means a hydrogen atom, a straight-chain or branched C₁-C₃₀ alkyl group, which optionally is interrupted by 1-15 oxygen atoms, and/or optionally is substituted with 1-10 hydroxy groups, 1-2 COOH groups, a phenyl group, a benzyl group and/or 1-5 -OR⁹ groups, with R⁹ in the meaning of a hydrogen atom or a C₁-C₇ alkyl radical, or -L¹-R^F,

L¹ means a straight-chain or branched C₁-C₃₀ alkylene group, which optionally is interrupted by 1-10 oxygen atoms, 1-5 -NH-CO groups, 1-5 -CO-NH groups, by a phenylene group optionally substituted by a COOH- group, 1-3 sulfur atoms, 1-2 -N(B¹)-SO₂ groups and/or 1-2 -SO₂-N(B¹)-groups with B¹ in the meaning of A¹, an NHCO group, a CONH group, an N(B¹)-SO₂ group or an -SO₂-N(B¹) group and/or optionally is substituted with radical R^F, and

R^F means a straight-chain or branched perfluorinated alkyl radical of formula C_nF_{2n}E, whereby n stands for number 4-30, and

E stands for a terminal fluorine atom, chlorine atom, bromine atom, iodine atom or a hydrogen atom,

and optionally present acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides, are used.

29. (Amended) Use according to claim [one of claims] 22 [to 28], wherein the following compounds are used:

-- 1,4,7-Tris(carboxylatomethyl)-10-(3-aza-4-oxo-hexan-5-yl)-acid-(2,3-dihydroxypropyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl)-amide]-

- 1,4,7-Tris(carboxylatomethyl)-10-((3-aza-4-oxo-hexan-5-yl)ic)acid-N-(3,6,9,12,15-pentaoxa)-hexadecyl-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-((3-aza-4-oxo-hexan-5-yl)ic)-acid-N-5-hydroxy-3-oxa-pentyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-((3-aza-4-oxo-hexan-5-yl)ic)-acid-[N-3,6,9,15-tetraoxa-12-aza-15-oxo-C₁₇-C₂₆-hepta-decafluor)hexacosyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)ic)-acid-N-(2-methoxyethyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex.

- 1,4,7-Tris(carboxylatomethyl)-10-((3-aza-4-oxo-hexan-5-yl)-acid-N-5-hydroxy-3-oxa-pentyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-((3-aza-4-oxo-hexan-5-yl)-acid-[N-3,6,9,15-tetraoxa-12-aza-15-oxo-C₁₇-C₂₆-hepta-decafluor)hexacosyl]-amide)-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)-acid-N-(2-methoxyethyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide)-1,4,7,10-tetraazacyclododecane, gadolinium complex.

- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)-acid-[N-3,6,9,15-tetraoxa-12-aza-15-oxo-C₁₇-C₂₆-hepta-decafluor)hexacosyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)-acid-N-(2-methoxyethyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex.

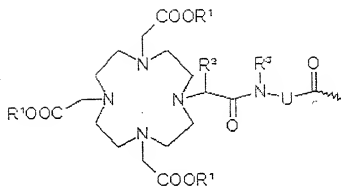
- 1,4,7-Tris(carboxylatomethyl)-10-[(3-aza-4-oxo-hexan-5-yl)-acid-N-(2-methoxyethyl)-N-(1H,1H,2H,2H,4H,4H,5H,5H-3-oxa)-perfluorotridecyl]-amide}-1,4,7,10-tetraazacyclododecane, gadolinium complex.

30. (Amended) Use according to claim [one of claims] 1 [to 7], wherein as perfluoroalkyl-containing metal complexes, the compounds with sugar radicals of general formula Ic



in which

R represents a mono- or oligosaccharide radical bonded by the 1-OH- or 1-SH-position,
R^F is a perfluorinated, straight-chain or branched carbon chain with the formula -C_nF_{2n+2}E,
in which E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen
atom, and n stands for numbers 4-30,
K stands for a metal complex of general formula IIc,



(IIc)

in which

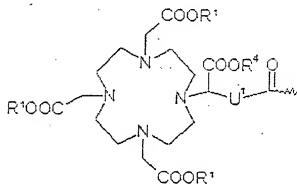
R^1 means a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70, provided that at least two R^1 stand for metal ion equivalents,

R^2 and R^3 , independently of one another, represent hydrogen, C_1 - C_7 alkyl, benzyl, phenyl, $-CH_2OH$ or $-CH_2OCH_3$, and

U represents $-C_6H_4-O-CH_2-\omega$, $-(CH_2)_{1-5}-\omega$, a phenylene group, $-CH_2-NHCO-CH_2-CH(CH_2COOH)-C_6H_4-\omega$, $-C_6H_4-(OCH_2CH_2)_{0-1}-N(CH_2COOH)-CH_2-\omega$, or a C_1 - C_{12} alkylene group or C_7 - C_{12} - C_6H_4-O group optionally interrupted by one or more oxygen atoms, 1 to 3 $-NHCO$ groups or 1 to 3 $-CONH$ groups and/or substituted with 1 to 3 $-(CH_2)_{0-5} COOH$ groups, whereby ω stands for the binding site to $-CO-$,

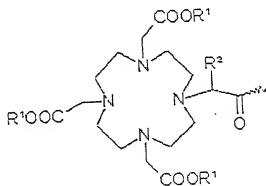
or

of general formula IIIc



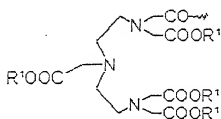
(IIIc)

in which R^1 has the above-mentioned meaning, R^4 represents hydrogen or a metal ion equivalent mentioned under R^1 , and U^1 represents $-C_6H_4-O-CH_2-\omega$, whereby ω means the binding site to $-CO-$, or of general formula IVc

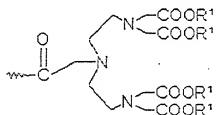


(IVc)

in which R^1 and R^2 have the above-mentioned meaning or of general formula VcA or VcB

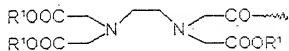


(VcA)



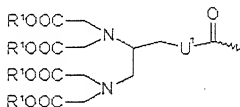
(VcB)

in which R^1 has the above-mentioned meaning, or of general formula VIc



(VIc)

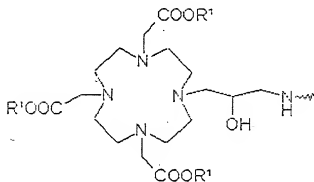
in which R^1 has the above-mentioned meaning, or of general formula VIIf



(VIIf)

in which R^1 has the above-mentioned meaning, and

U^1 represents $-C_6H_4-O-CH_2-\omega$, whereby ω means the binding site to $-CO-$ or of general formula VIIIc

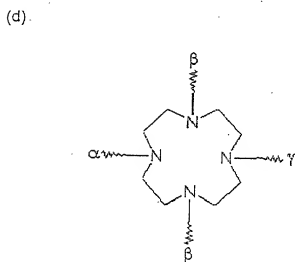
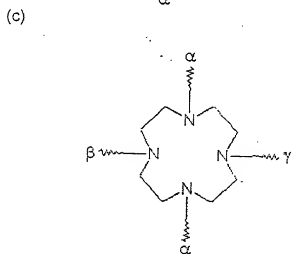
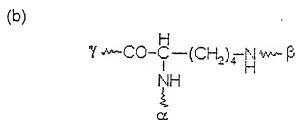
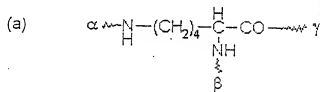


(VIIIc)

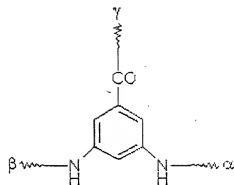
in which R^1 has the above-mentioned meaning,

and in radical K, optionally present free acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides,

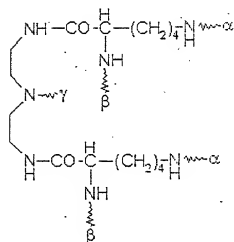
G for the case that K means metal complexes IIc to VIc represents a radical that is functionalized in at least three places and is selected from the following radicals a) to j)



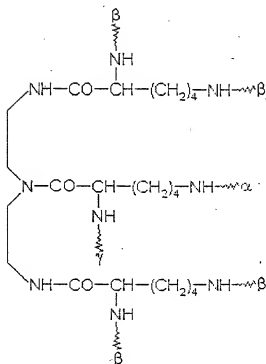
(e)



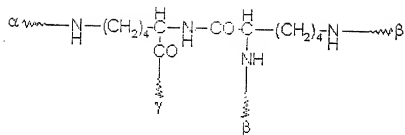
(f)



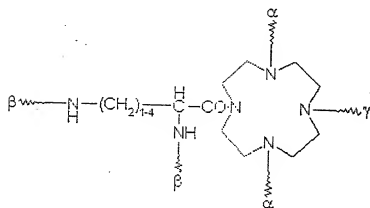
(g)



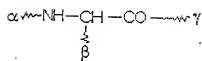
(h)



(i)



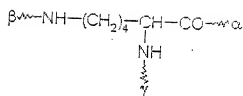
(j)



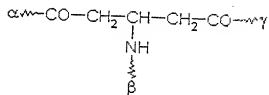
and

G for the case that K means metal complex VIIIc represents a radical that is functionalized in at least three places and is selected from k) or l),

(k)



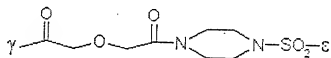
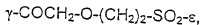
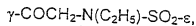
(l)



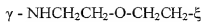
whereby α means the binding site of G to complex K, β is the binding site of G to radical Y, and γ represents the binding site of G to radical Z,

Y means $-\text{CH}_2$, $\delta - (\text{CH}_2)_{(1-5)}\text{CO}-\beta$, $\delta - \text{CH}_2 - \text{CHOH} - \text{CO} - \beta$ or $\delta - \text{CH}(\text{CHOH} - \text{CH}_2\text{OH}) - \text{CHOH} - \text{CHOH} - \text{CO} - \beta$, whereby δ represents the binding site to sugar radical R and β is the binding site to radical G,

Z stands for



or



whereby γ represents the binding site of Z to radical G, and ξ means the binding site of Z to perfluorinated radical R^{F}

and

l^1, m^1 , independently of one another, mean integers 1 or 2, and

p^1 means integers 1 to 4, are used.

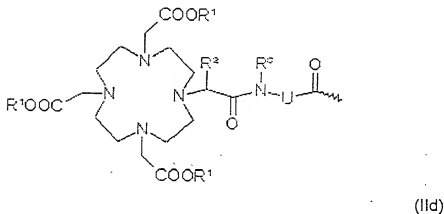
37. (Amended) Use according to claim [one of claims] 1 [to 7], wherein as perfluoroalkyl-containing metal complexes, the compounds with polar radicals of general formula Id



in which

R^{F} is a perfluorinated, straight-chain or branched carbon chain with formula $-\text{C}_n\text{F}_{2n}\text{E}$, in which E represents a terminal fluorine, chlorine, bromine, iodine or hydrogen atom, and n stands for numbers 4-30,

K stands for a metal complex of general formula IId,



in which

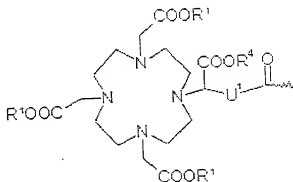
R^1 means a hydrogen atom or a metal ion equivalent of atomic numbers 23-29, 42-46 or 58-70, provided that at least two R^1 stand for metal ion equivalents,

R^2 and R^3 , independently of one another, represent hydrogen, C_1 - C_7 alkyl, benzyl, phenyl, $-CH_2OH$ or $-CH_2OCH_3$, and

U represents $-C_6H_4-O-CH_2-\omega$ -, $-(CH_2)_{1-5}-\omega$ -, a phenylene group, $-CH_2-NHCO-CH_2-CH(CH_2COOH)-C_6H_4-\omega$ -, $-C_6H_4-(OCH_2CH_2)_{0-1}-N(CH_2COOH)-CH_2-\omega$ -, or a C_1 - C_{12} alkylene group or C_7 - C_{12} - C_6H_4-O group optionally interrupted by one or more oxygen atoms, 1 to 3 $-NHCO$ groups, 1 to 3 $-CONH$ groups and/or substituted with 1 to 3 $-(CH_2)_{0-5}COOH$ groups, whereby ω stands for the binding site to $-CO-$,

or

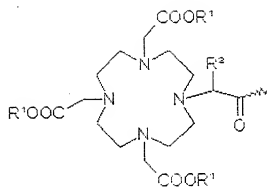
of general formula IIIId



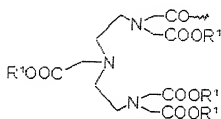
(IIIId)

in which R^1 has the above-mentioned meaning, R^4 represents hydrogen or a metal ion equivalent mentioned under R^1 , and U^1 represents $-C_6H_4-O-CH_2-\omega$ -, whereby ω means the binding site to $-CO-$, or

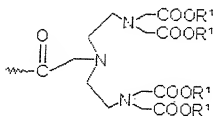
of general formula IVd



in which R¹ and R² have the above-mentioned meaning, or of general formula VdA or VdB



(VdA)



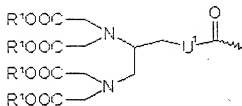
(VdB)

in which R¹ has the above-mentioned meaning, or of general formula VId



(VId)

in which R¹ has the above-mentioned meaning, or of general formula VIId



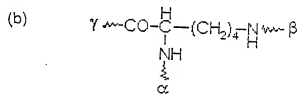
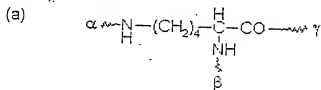
(VIId)

in which R¹ has the above-mentioned meaning, and

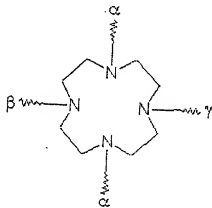
U¹ represents -C₆H₄-O-CH₂-ω-, whereby ω means the binding site to -CO-,

and in radical K, optionally present free acid groups optionally can be present as salts of organic and/or inorganic bases or amino acids or amino acid amides,

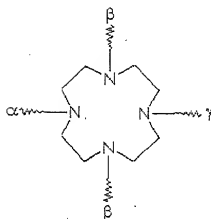
G represents a radical that is functionalized in at least three places and is selected from the following radicals a) to g)



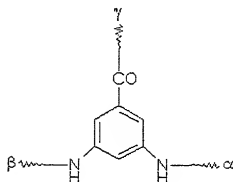
(c)



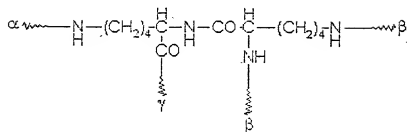
(d)



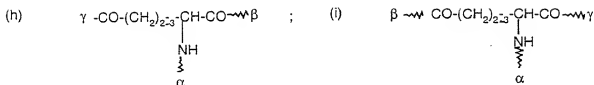
(e)



(f)

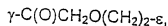


(g)



whereby α means the binding site of G to complex K, β is the binding site of G to radical R, and γ represents the binding site of G to radical Z

Z stands for



whereby γ represents the binding site of Z to radical G and ξ means the binding site of Z to perfluorinated radical R_ξ

R represents a polar radical that is selected from complexes K of general formulas II d to VII d, whereby R^1 here means a hydrogen atom or a metal ion equivalent of atomic numbers 20, 23-29, 42-46 or 58-70, and radicals R^2 , R^3 , R^4 , U and U^1 have the above-indicated meaning,

or

means the folic acid radical

or

means a carbon chain with 2-30 C atoms that is bonded to radical G via -CO-, or SO₂- or a direct bond and is straight or branched, saturated or unsaturated,

optionally interrupted by 1-10 oxygen atoms, 1-5 -NHCO groups, 1-5 -CONH groups, 1-2 sulfur atoms, 1-5 -NH groups or 1-2 phenylene groups, which optionally can be substituted with 1-2 OH groups, 1-2 NH₂ groups, 1-2 -COOH groups, or 1-2 -SO₃H groups,

or

optionally substituted with 1-8 OH groups, 1-5 -COOH groups, 1-2 SO₃H groups, 1-5 NH₂ groups, 1-5 C₁-C₄ alkoxy groups, and

l¹, m¹, p², independently of one another, mean integers 1 or 2 are used.

44. (Amended) Use according to claim [one of claims] 37[-43], wherein the gadolinium complex of 2,6-N,N'-bis[1,4,7-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecane-10-(pentanoyl-3-aza-4-oxo-5-methyl-5-yl)]-lysine-[1-(4-perfluorooctylsulfonyl)-piperazine]-amide is used.

45. (Amended) Use according to claim [one of claims] 1[-7], wherein as perfluoroalkyl-containing metal complexes, galenic formulations that contain paramagnetic, perfluoroalkyl-containing metal complexes of general formulas I, Ia, Ib, Ic and/or Id and diamagnetic perfluoroalkyl-containing substances, preferably dissolved in an aqueous solvent, are used.